CHILDREN'S REACTIONS TO PSYCHOTOMIMETIC DRUGS

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In this paper I shall discuss some of my rather extensive experiences with both amphetamine (Benzedrine®) and LSD in children.

I started as a child psychiatrist in the early 1930's in the Bellevue psychiatric children's wards with children under the age of 13. At that time the post-encephalitic disorders following the epidemic of encephalitis were still observable. Those were the model for the concept of the hyperkinetic child, or the brain-driven child. That concept has remained until today, although I was convinced very early that the hyperkinetic child is not a child who has a problem with increased motor activity, or with increased physical energy, or with increased impulses, but rather that it is a problem of perceptual disorganization.

I came to these conclusions from my use of the Visual Motor Gestalt Test (Bender, 1938) and many other kinds of perceptual tests, such as the block design and the weight evaluation test in the Stanford-Binet Scale, and particularly the body image test in the drawing of a man.

The hyperkinetic child is one who has difficulty in organizing his perceptual experiences, in getting a body image concept and in getting, therefore, a self-image concept. Consequently, his restlessness is due to searching and seeking movements which lead him to contact the world about him in every way that he can, by moving about, by grasping things with his hands, or by biting, sucking or tasting with his mouth. Such behavior, of course, is quite distracting to the child himself and may prove to be destructive and aggressive.

The child who is hyperkinetic on the basis of cerebral pathology is seen to be a child with maturational lags; his behavior is immature, disorganized, and not goal directed. We do not wish to reduce the amount of activity but rather to enhance the pattern of activity, including a goal, and maturation. Thus, organization of behavior should be both cross-sectional and longitudinal.

At that time we were seeking a medication that would help with these children. Bradley and Bowen (1940, 1941) had used amphetamine in large doses of 20, 30, 40 and 50 mg per day in children, and claimed that it was useful in the hyperkinetic child with organic brain disease.

We were also interested in finding a drug that would help us with the sexually stimulated children, of which we had a number at that time. Paul Schilder (1938) had found in his psychoanalytic practice that if amphetamine was given to an adult who was under pressure to finish writing by a deadline, for example, it would be effective for the purpose given, but would also lead to a suppression of sexual interests and capacities; it was, therefore, not particularly liked by many such people.

And we were also concerned about children, particularly Negro boys, who were poor achievers, were not learning, and were, one might say, "sleeping in the noonday sun." That is, they tended to sleep in any situation of stress or boredom. They reminded us of cases of narcolepsy. Consequently, we used amphetamine for these problems.

When we gave amphetamine in the doses that Bradley recommended, we found that many children reacted with autonomic nervous system disorders, pallor and vomiting, and became very distraught, breaking windows, etc. Therefore, we lowered the dose and started out with a routine in which we gave 5 mg one morning, 10 the next, and 15 the next, then 20, and then stabilized the daily dosage at that level. For children under seven years we halved this dosage routine, while some robust children tolerated and benefited by doubling it. This is a routine which I have now used for these many years.

Occasionally there are children who still exhibit autonomic nervous system disorders and some tendency to sleeplessness, loss of appetite, and weight loss. This will pass off in a few days, or, at the most, in 10 days to two weeks. If one is patient and persists with the drug, one can get most children to tolerate it very well.

This drug will affect the children in such a way that they are relieved of a great deal of tension and anxiety, have a better learning capacity, and get along much better, both with peers, teachers and other authoritative figures. They feel more highly valued, better loved, better appreciated and more capable of doing things, and they advance more rapidly in the learning processes. If we arranged tutoring, a good school program, or any therapeutic or remedial program that the child needed, the child would advance.

The sexual problems simply melted away. Excessive sexual drives and preoccupations in a prepuberty child gradually disappeared. The child quit talking about them, then denied them and soon forgot them, or became amnestic for them. This is a process which happens normally in children, but the drug facilitates it. The hyperkinetic child becomes quieter because his behavior pattern is better organized and directed towards the normal goals of childhood, *i.e.*, learning and experiencing life.

We have been able to give this drug for weeks, months, and in some cases two and three years. We have never seen anything in the way of an amphetamine psychosis. Furthermore, and even more interesting, anything in the way of tolerance is rarely seen, so that it did not become ineffective, and it was not necessary to increase the dose. Also the drug can be stopped without getting any kind of withdrawal symptoms or effects. Whatever the child had gained would have grown into his system or built into his developmental pattern, and he would not regress to his former behavior.

For years before the new psychotropic drugs became available, the amphetamines were our most effective drugs in the modification of behavior in children with problems.

Recently a very interesting paper by Keith Connors (1966) of the Johns Hopkins University has reported the effects of *d*-amphetamine (Dexedrine®) on rapid visual discrimination and motor control in hyperkinetic children under mild stress. He used sophisticated test procedures and concluded that motor control was in no way affected, and that there were more organized perceptual responses in rapid visual discrimination together with an improvement in clinical symptomatology and school performance in a number of test measures.

Connor's conclusions confirm my experiences and convictions that the hyperkinetic child's basic problem is one of organization of perceptual experiences, and that the amphetamines are effective in modifying the behavior of children by facilitating perceptual organization.

That children never get a schizophrenic-like psychosis from amphetamine is partly due to the fact that childhood schizophrenia is not like adult schizophrenia. Children with schizophrenia do not experience hallucinations of the projected type like adults, but only of the introjected type. Children hear voices inside their head or other parts of the body, feel that they originate inside themselves and do not feel persecuted by them. Children get projected hallucinations in some toxic delirious states or in some neurotic situations, but not in schizophrenia. I have never known of a child to experience hallucinations of any kind because of amphetamine medication.

We also used, as the years went by and new drugs came in, all of the antihistamines, reserpine, meprobamate, energizers, phenothiazines and anti-

convulsants (Bender and Nichtern, 1956; Bender and Faretra, 1961) and found that these drugs in general do not sedate children, except temporarily, that they do not quiet them down in the sense of quieting down motor overactivity, but that they help them to organize their behavior, to pattern it more completely and to maturate more satisfactorily. Occasionally a large dose is given intravenously to control a major disturbance in a child. Children rarely get side effects with the drugs. The psychotropic drugs can be given in larger doses to children than to adults. We do not find any difficulty in stopping the drugs since children rarely show withdrawal symptoms.

My experience with LSD has been since 1961 at the Children's Unit of Creedmoor State Hospital (Bender *et al.*, 1962). I started in 1961, when Paul Hoch was Commissioner of the Department of Mental Hygiene in New York. He was very much opposed to the use of LSD to produce psychotic episodes as a method of therapy, and we had some difficulty in getting him to let us use the drug on children, until we convinced him that we did not want to use it because of its known psychotomimetic effects, but because it was known to inhibit serotonin, and as an agent, to quote Brodie (1958) which would cause "arousal and increased responsiveness to sensory stimuli, preponderance of sympathetic activity and increased skeletal and muscle tone and activity."

These are the basic features which I think define schizophrenia in childhood. In childhood schizophrenia, all boundaries are lost, not only of the psychological and personality experiences, but also those of the visceral functions, autonomic nervous system, vascular tone, muscular tone and perception.

It was hoped that the LSD would be effective in correcting these disorders. We started out with it very carefully because of the two warnings that we had: one, that the children would become disturbed, and the other, that repeated use of the drug would lead to tolerance. So we gave it once a week in small doses, 25 μg intramuscularly, to prepuberty children, 5 to 11 years of age. Two children between 10 and 11 years of age did become panicky and anxious; we immediately stopped the effects of the drug in these two children with sodium amytal. None of the other children became disturbed. They all showed a tendency to become "high" and lively. Where they were pale and blue-lipped before, they developed a bright, pink color, eyes were bright, and they looked up. They tried to make a contact with us for expressions of affection, and to engage in motor play. These were mute, autistic, schizophrenic children. And they showed a general improvement in well-being, appearance, and lift in mood.

We worked with these children, gradually increasing the dose and the frequency until we were giving 150 μg per day orally in two divided doses

morning and evening, and continued this for weeks, months, and in some cases for a year or two. We meanwhile were making all kinds of psychological, clinical and biological studies.

We gave this first to young, autistic children, and we found that we were able to get an improvement in their general well-being, general tone, habit patterning, eating patterns and sleeping patterns, and we could raise the Vineland Social Maturity score, which is the behavior evaluation score. In a few children we got some more vocalization, although not actually any improvement or increase in language as such (Bender *et al.*, 1962; 1963). We soon gave it also to older autistic children and got somewhat less beneficial effects, since these were more chronic, and complicated with more organicity in some cases.

We then gave LSD in the same doses to non-autistic schizophrenic boys 6 to 12 years of age. They were intelligent and verbal and could be tested psychologically and in psychiatric interviews (Bender *et al.*, 1963). They were selected because they had typical schizophrenic psychosis, with flying fantasies and identification and body image difficulties, loose ego boundaries, introjected objects and voices and bizarre ideologies. They had obvious anxiety and labile vaso-vegetative functions. After administering LSD to these children we found results contrary to those reported in adults. These children became more insightful, more objective, more realistic; and in a short time they became frankly depressed for reality reasons. They noted they were in the hospital, that they were away from their family, and that they had had "crazy" ideas before.

These were children who were not subjected to special psychotherapy but only to our usual activity program. They all benefited sufficiently so that those who did have a place to go were in some months able to return to their homes and community schools.

We also tried LSD on two adolescent boys who were mildly schizophrenic (Bender, 1966*a*). These were boys whom we had known for many months. When we gave the first dose of 100 μg of LSD orally, Dr. Faretra and I sat opposite the boys for two hours, encouraging them to talk and to draw. Within a half hour they began to report distortions in visual experiences, such things as claiming that we were grimacing at them, smiling at them, and making faces at them, that the other boy's face was turning green, that the lines in their corduroy pants were getting too numerous and were moving around, and that the pencils they were using were getting rubbery. These by and large represented fluidity or motility in visual experiences that they really had. There were no hallucinations.

They became disturbed to the extent that they said we were experimenting on them. In two or three hours this passed off, and the next day we put

them back into their group activity after repeating the dose; they had no trouble that day as long as they were in their own group and away from close observation of the psychiatrist.

We continued these boys for some months on 150 μg in two divided doses daily. One of them benefited very much, and was able to go home and return to school, although he has since returned as a disturbed adult schizophrenic.

The other one had been tried many times out of the hospital in foster homes, without success. After some months he complained that we were experimenting on him with the drug and trying to keep him from getting out of the hospital. We discontinued the drug. That was not because of the drug but because of the boy's attitude toward it, based on his own psychopathology.

We also used methysergide (UML, Sansert®) in daily doses of two or three 4 mg space tabs. This is a methylated derivative of LSD which is used to prevent migraine headaches. We found that it had effects similar to LSD on schizophrenic children.

Gloria Faretra and I (1965) did a study, using the Funkenstein Test on the autonomic nervous system, of a series of children. We were able to show that LSD, methysergide and psilocybin have a normalizing effect upon the labile plastic autonomic system characteristic of schizophrenic children.

We used LSD on 89 children from January 1961 to July 1965, when Sandoz no longer made it available for research purposes. We were unwilling to apply to N.I.M.H. for supplies at that time because of the reports of chromosome damage in LSD users. We immediately started examining the chromosomes of the children who had received LSD and methysergide, although it was up to two years after termination of the drugs. We were not able to confirm that there was chromosome damage in any of those children that we had examined (Bender and Sankar, 1968).

We hope to go back to using LSD because we have found that it is one of the most effective methods of treatment we have for childhood schizophrenia. It tends to normalize the labile, boundaryless physiological, perceptual and psychological functions in schizophrenic children, and helps them to a more normal physiological, psychological and social adjustment.

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DISCUSSION

DR. WEST: You say you started out with a dose in the small children of 25 μg of LSD per week. You gave them one dose a week, and the effects that you noted—

DR. BENDER:—Only lasted a few hours.

DR. WEST: But then you said you went up to 150 μg per day?

DR. BENDER: Yes. We increased it gradually to test its safety, and to avoid disturbances. Finally we gave 150 μg daily in two divided doses. We saw no evidence of anything that was called tolerance, unless you speak of tolerance in terms of the fact they did not become disturbed as adults do.

They showed no evidence of tolerance in terms of the effects upon the stabilizing or normalizing of the autonomic nervous system and general well-being.

Ongoing biochemical studies by Dr. Sankar showed a binding of serotonin and histamine and freeing of epinephrine. This progressed for some weeks, tended to level off to a plateau and continued on a plateau thereafter, indicating some tolerance (Sankar *et al.*, 1964).

Another study (Bender 1966*b*) was done by several of the doctors (D. Winn, J. Dowling, G. Dooher) involving six pairs of matched prepuberty schizophrenic boys who received the usual dose of LSD. From the first day, they watched them carefully, asking for every possible subjective reaction, as well as doing psychiatric interviews on selected psychological, sensory and neurological tests. They did find that some children were mildly disturbed the first day, and could find in half of the children some kind of sensory disorder. In all but two, this disappeared by the second day. And in one it lasted as long as 10 days, but beyond that there was no further disorder.

So, there is evidence that there are disturbances that occur the first day, which you can play down if you leave the child in the usual routine. Or you can emphasize them if you look for them very carefully. As for the tolerance to the physiological effects, this appears, from laboratory evidence, about the end of the third or fourth week, and then reaches a plateau. Clinically, changes are seen to continue for months and are integrated into a more healthy and mature level in the development of the child.

DR. FREEDMAN: Did you have a large pupil with LSD?

DR. BENDER: Yes. The pupils were examined during the time we did the Funkenstein Test, and on many other occasions, and in two-thirds of the children they showed large pupils after the first dose.

DR. FREEDMAN: And did that occur after every dose, or do they get tolerant?

DR. BENDER: Some children, but not all, became tolerant to that.

DR. FREEDMAN: Of course, the definition of tolerance has to do a great deal with correlates with autonomic tolerance. That is, tolerance to mydriasis, and tolerance to mental effects in man. It may be that they showed tolerance in that respect.

DR. BENDER: Yes.

DR. HOLMSTEDT: There's one thing here which I find disturbing. You say that you get as good effects with methysergide, and that it produces no hallucinations whatsoever.

DR. BENDER: Well, so it is sometimes said. Actually, it is known to be an hallucinogen, although not as strong as LSD. It has also been used by some "hippies" in California. I am a migraine headache sufferer and have found it a very effective preventive. But I assure you that I experienced

perceptual, especially visual, distortions when I first started the medication and when I make a mistake and take a double dose.

DR. MANDELL: I know of some differing data, Dr. Bender, and it perhaps has to do with the diagnostic heterogeneity of your population. Dr. Simmons at U.C.L.A. used the Rimland Scale criteria for autistic children and, on the basis of your work with Dr. Faretra on LSD, tried this on autistic children three times a week. He found, in general, only a little bit of drug induced an increase in activity. In general, after several treatments, the U.C.L.A. group saw no more increase in tendency to talk, to relate, or to make contact. Studying this group over several months, they failed to duplicate your findings. But, on the other hand, it may have been some function of the heterogeneity of your group of children versus this rather homogeneous group that they were working with.

DR. BENDER: I thing Rimland's Scale is a pretty rigid scale, and I suspect many of his cases are also organic as well as schizophrenic, or perhaps only organic. Also, you only gave LSD three times a week. We gave it daily.

DR. LEHRER: Dr. Bender, when you first started with amphetamine, I assume that it was the racemic amphetamine

DR. BENDER: We never use Dexedrine (*d*-amphetamine) because in the city and state hospital Benzedrine is the drug that is available, and we soon learned to use it so well we had no reason for shifting over to Dexedrine. I have known some doctors who in their private practice used Dexedrine, and they claimed they didn't get as good results.

DR. LEHRER: I was wondering whether some of the vomiting and other concomitants may not have been due to the *levo* component?

DR. BENDER: Well, that may have been.

DR. GESSNER: Dr. Bender, could you tell us whether you sometimes used methysergide together with LSD?

DR. BENDER: We never used them both at one time on the same patient. We used them on different patients, and there were times when we shifted from methysergide to LSD because methysergide did occasionally have side effects, *e.g.*, causing ergot effects in the vascular system, especially of the legs. We had that in three or four of the children, and consequently changed them over to LSD. Also, we had to give up LSD earlier than methysergide. So, some of the children that were getting LSD were continued on methysergide. We never gave both drugs at the same time to one child.

DR. GESSNER: I asked my question simply because Sai-Halasz had reported methysergide to potentiate the effects of hallucinogens (Sai-Halasz, A.: *Experientia, 18:* 137–138, 1962).